

GP 1205

71477 U.S. PTO  
04/24/97

Case No. 900-9523/C2/D2/C1

#10  
1 of 3  
JGL  
5/22/97

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :  
MAXIMILIAN GRASSBERGER, et al. : Art Unit: 1205  
Serial No. 08/471,146 : Examiner: J. Goldberg  
Filed: June 6, 1995 :  
For: NEW USE OF 11,28-DIOXA-4- :  
AZATRICYCLO[22.3.1.0<sup>4,9</sup>] :  
OCTACOS-18-ENE DERIVATIVES :  
AND PHARMACEUTICAL COMPO- :  
SITIONS CONTAINING THEM :

I hereby certify that this correspondence is being  
deposited with the United States Postal Service as  
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sistant Commissioner for Patents, Washington, D.C.  
20231, on April 22, 1997  
(Date of Deposit)  
Thomas O. McGovern  
Name of Person Signing  
Thomas O. McGovern  
Signature  
April 22, 1997  
Date of Signature

BRIEF FOR APPELLANTS

Assistant Commissioner for Patents  
Washington, D.C. 20231

MAY 20 1997

. Dear Sir:

This is an appeal from the final rejection of claims 13  
to 26 in the above identified application.

REAL PARTY IN INTEREST

The real party in interest in the instant Appeal is  
NOVARTIS AG, a company organized under the laws of the Swiss  
Confederation, of 4002 Basle, Switzerland.

RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to  
Appellants, Appellants' legal representatives, or assignee  
which will directly affect or be directly affected by or have  
a bearing on the Board's decision in the pending appeal.

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### STATUS OF THE CLAIMS

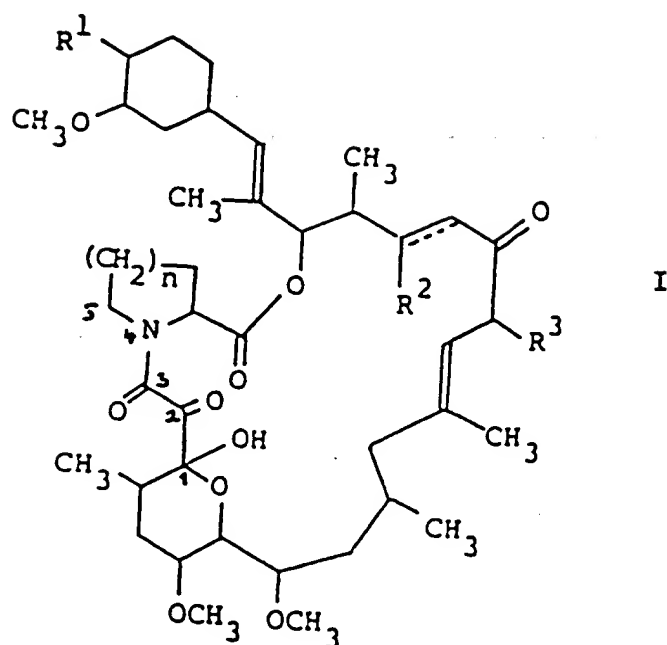
Claims 1 to 12 were originally presented for examination. In response to a restriction requirement in the Office Action of October 25, 1995, claims 1 to 12 were canceled from the application and replaced with claims 13 to 26 by an Amendment dated April 29, 1996. In order to simplify the issues in the present appeal, Appellants are enclosing with this Brief an Amendment under 37 CFR 1.116 to cancel claims 13 to 18 from the appeal. The claims now on appeal are claims 19 to 26 as set out in attached Appendix A.

### STATUS OF AMENDMENTS

Appellants presented claims 27 and 28 in the Amendment under 37 CFR 1.116 of December 23 1996 in response to the final Office Action of July 23, 1996. In the Examiner's Advisory Action, dated January 23, 1997, the Examiner indicated that the Amendment would not be entered, because a corresponding number of finally rejected claims were not canceled from the application.

### SUMMARY OF THE INVENTION

The present invention is directed to pharmaceutical compositions for topical administration in the form of a lotion, gel, or cream comprising 1% to 3% of a compound of the formula



wherein

$R^1$  is optionally protected hydroxy,

$R^2$  is hydrogen or optionally protected hydroxy,

$R^3$  is methyl, ethyl, propyl or allyl,

$n$  is 1 or 2 and

the symbol of a line and dotted line is a single bond or a double bond,

in free form or in pharmaceutically acceptable salt form, and a pharmaceutically acceptable topical carrier for a lotion, gel, or cream. The compositions are useful in topically treating inflammatory or hyperproliferative skin diseases or cutaneous manifestations of immunologically-mediated illnesses, such as psoriasis, atopic dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, Lichen planus, Pemphigus, bullous Pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematosus or Alopecia areata.

## ISSUES

### A. Obviousness-type Double Patenting Rejection

Claims 19 to 26 are rejected for obviousness-type double patenting over the claims of U.S. Patent No. 5,366,971, which issued on November 22, 1994. To overcome this rejection, Appellants' are enclosing with this Brief a Terminal Disclaimer in accordance with the requirements of Rule 78(d) and Rule 321(b), to disclaim the portion of the term of any patent, that issues on the present application, which extends beyond November 22, 2011, the expiration date of United States Patent 5,366,971. The disclaimer also states that any patent issuing on this application shall be enforceable only for and during such period that the ownership of this patent is the same as the ownership of USP 5,366,971.

### B. Rejection under 35 USC 103

The relevant issue now in the instant rejection is whether the Fujisawa European Patent Application, EPA 0 184 162, would motivate one skilled in the art to prepare lotions, gels, or creams containing the agents of the reference for use in topically treating the organ transplant resistance, graft-versus-host disease, autoimmune diseases, and infectious diseases disclosed by Fujisawa. The Examiner argues that Fujisawa clearly teaches the use of Appellants compounds for treating lupus erythematosus by external administration on page 67, line 3, and page 76,

line 15. The Examiner concludes that in view of this, one skilled in the art would be motivated to prepare topical compositions containing the prior art compounds for treating Lupus erythematosus; and therefore, the claimed topical compositions are obvious over EPA 0 184 162.

#### GROUPING OF THE CLAIMS

The ground of rejection in this appeal applies to the topical pharmaceutical compositions of claims 19 to 26.

#### ARGUMENT

It will be noted that the indication "Lupus erythematosus" referred to on page 67, line 3, of the Fujisawa reference is "systemic Lupus erythematosus"; not the cutaneous manifestations of the condition. Fujisawa clearly had no conception that its compounds could be used topically for the treatment of the cutaneous manifestations of Lupus erythematosus. Indeed, all of the conditions disclosed by Fujisawa require systemic treatment; and in all of the examples of the reference, the compounds are administered orally or parenterally, that is, systemically. There is no example of a condition, which can be treated locally; and even the fungi used in the antimicrobial test 2, *Aspergillus fumigatus* and *Fusarium oxysporum*, are organisms which are treated systemically. No testing was carried out with organisms, such as dermatophytes or yeast fungus, which would show topical efficacy. This is not surprising. As discussed on pages 2 and 3 of the instant specification, the topical

efficacy of the claimed compounds is totally unexpected in light of the results found with the known cyclic immunosuppressant, cyclosporine. There is clearly nothing in the art as a whole or in Fujisawa, which would suggest that, unlike cyclosporin, the claimed compounds would exhibit surprising topical activity; and there is certainly nothing which could possibly motivate one skilled in the art to investigate the topical treatment of the conditions disclosed by Fujisawa, all of which require systemic treatment. From the teachings of the Fujisawa reference, one skilled in the art would recognize that the external administration contemplated by the reference clearly involves those modes of administration, such as the nasal, buccal, rectal, etc. routes, which would produce a systemic effect. Fujisawa's pharmaceutical forms listed on page 76, lines 18 and 19, include forms, such as suppositories, which can only be used for administration by these systemic modes. Appellants' lotions, gels, and creams, on the other hand, cannot be used in any of these routes or for systemic administration of a drug. No one would reasonably try to treat organ transplant resistance, graft-versus-host disease, autoimmune diseases, and infectious diseases systemically by topically administering a drug in a lotion, gel, or cream at a site distant from the point where it is supposed to exert its activity. The purpose of topical administration with these forms is to obtain a non-systemic beneficial effect at the site of administration. Fujisawa does not disclose a single utility for the claimed compounds which can beneficially be treated locally; and the cyclosporin art teaches that such compounds are generally not effective when administered in

conventional topical forms. It is clear that Appellants' pharmaceutical compositions could only be arrived at by disregarding the substance of Fujisawa's teachings and the prior art as a whole. There is no way that one skilled in the art guided by Fujisawa's disclosure and examples would be led to Appellants' topical compositions or uses without direction from the instant application. The Court of Customs and Patent Appeals indicated In re Taborsky (183 USPQ 50), that for obviousness, the prior art must provide one with motivation to make the modifications needed to arrive at the claimed invention. In the present case, it cannot reasonably be said that the Fujisawa reference would motivate one to prepare topical formulations which could not be used to treat the conditions disclosed by the reference. Fujisawa, in effect, fails to provide the utility required for motivation and obviousness. Appellants submit that the presently

- claimed topical compositions are patentable over the Fujisawa application; and accordingly, the Examiner's rejection of
- claims 19 to 26 under 35 USC 103 should be reversed.

It is respectfully requested that the period for filing the Appeal Brief on the above identified application Serial No. 08/471,146 originally set to expire February 23, 1997 be extended for two months to April 23, 1997.

Please charge the following fees to Deposit Account No. 19-0134 in the name of Sandoz Corporation: i) the Appeal Brief fee of \$300.00 required by 37 CFR 1.17(f); ii) the extension fee of \$390.00 required by 37 CFR 1.17(b); and iii) the terminal disclaimer fee of \$120.00 required by 37 CFR 1.20(d).

Respectfully submitted,

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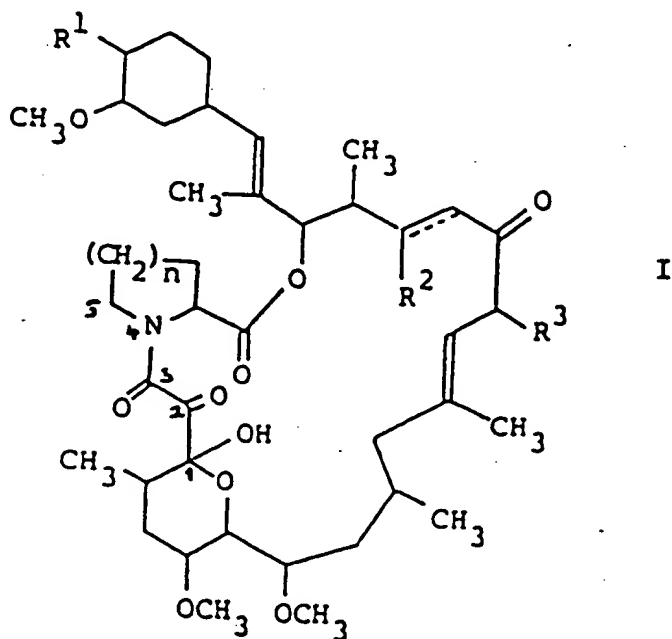
April 22, 1997

Enclosures: Copies of Brief (3);  
Amendment under 37 CFR 1.116;  
Terminal Disclaimer;  
Two month Extension of Time;  
Page 8 of Brief in triplicate;  
Appendix A ( pages);  
COM Stamp; Postcard.



APPENDIX A

19. A pharmaceutical composition for topical administration in the form of a lotion, gel, or cream comprising 1% to 3% of a compound of the formula



wherein

$R^1$  is optionally protected hydroxy,

$R^2$  is hydrogen or optionally protected hydroxy,

$R^3$  is methyl, ethyl, propyl or allyl,

$n$  is 1 or 2 and

the symbol of a line and dotted line is a single bond or a double bond,

in free form or in pharmaceutically acceptable salt form, and a pharmaceutically acceptable topical carrier for a lotion, gel, or cream.

APPENDIX A

20. A pharmaceutical composition according to claim 19, wherein,

$R^3$  is propyl or allyl, and  
the symbol of a line and dotted line is a single bond,  
in free form or in pharmaceutically acceptable salt form.

21. A pharmaceutical composition according to claim 19, wherein  $R^1$  and  $R^2$  are hydroxy,

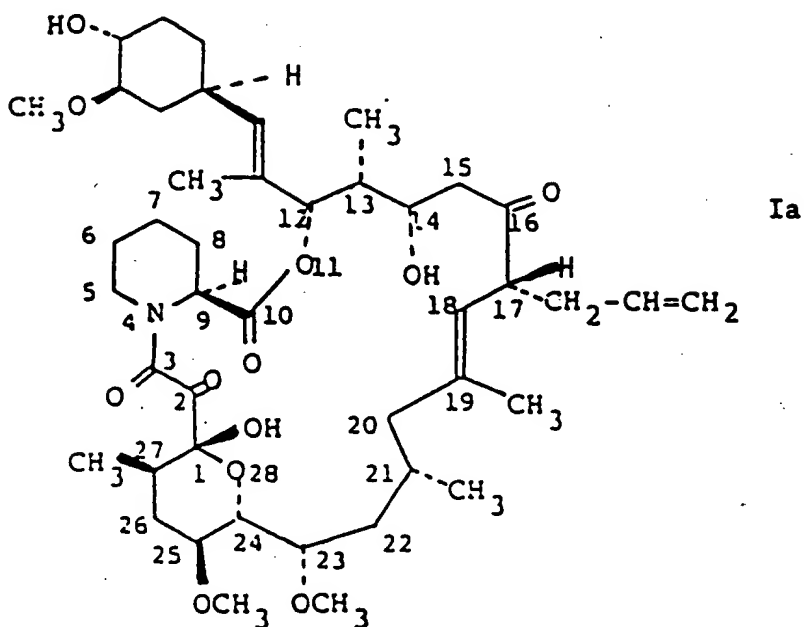
$R^3$  is propyl or allyl,  
 $n$  is 2, and  
the symbol of a line and dotted line is a single bond, in  
free form or in pharmaceutically acceptable salt form.

22. A pharmaceutical composition according to claim 19, wherein  $R^1$  and  $R^2$  are hydroxy,

$R^3$  is allyl,  
 $n$  is 2, and  
the symbol of a line and dotted line is a single bond, in  
free form or in pharmaceutically acceptable salt form.

APPENDIX A

23. The pharmaceutical composition according to claim 19 in which the compound is



in free form.

24. A pharmaceutical composition according to claim 19 in which the composition is a lotion.

25. A pharmaceutical composition according to claim 19 in which the composition is a gel.

26. A pharmaceutical composition according to claim 19 in which the composition is a cream.